REMARKS

In the Office Action of December 31, 2003, restriction was required between the claims drawn to certain compounds, to kits, to methods for reversal of neuromuscular block and to pharmaceutical compositions.

Applicants provisionally elected with traverse to prosecute claims 11-14 in Group III directed to a method for reversing a neuromuscular block. Applicants further, for purpose of preliminary examination, elected γ-cyclodextrin as the chelator, although the full scope of the elected claims are understood to be examined after determining the patentability of the γ-cyclodextrin embodiment.

Applicants confirm their election of Group III, claims 11-14, with traverse. Applicants respectfully traverse the election requirement and submit that Group IV, claims 15-19, drawn to pharmaceutical compositions used in the method of the elected claims should be examined as well, being related as composition and method of using.

Applicants confirm the elect of γ-cyclodextrin as the elected species for preliminary examination.

In the Office Action of December 31, 2003, the Examiner rejected claims 11-13 under 35 U.S.C. 112, first paragraph, for lack of enablement. The Examiner concluded that the specification

did not provide enablement for all neuromuscular blocking drugs with all cyclodextrin.

The rejection under 35 U.S.C. 112, first paragraph, is respectfully traversed, particularly in view of the present amendments. The claims are now directed to the reversal of a drug-induced neuromuscular block in a patient caused by a depolarizing or non-depolarizing neuromuscular blocking agent without causing an increase in the level of acetylcholine. This is the effective result of the guest-host complex recited in the claim whereby the chemical chelator bonds with the neuromuscular blocking agent. Chemical chelators to be used according to the invention are well defined in the specification. Guest-host complex is also defined in the specification, on page 3, in the fourth full paragraph:

> "The term chemical chelator (or sequestrant), as used in the present invention, means any organic compound which can engage in host-guest complex formation with a neuromuscular blocking agent. The chemical chelator acts as the host molecule, the neuromuscular blocking agent being the guest molecule. The specific molecular complex, the guest-host complex, is defined as an organised chemical entity resulting from the association of two or more components held together by noncovalent intermolecular forces."

Such chelators are well known to the ordinary practitioners in the art. A substantial number of examples are also provided in the specification.

The Examiner cited the DÉSIRÉ et al publication for teaching that the neuromuscular blocking effect of sarin and soman may be reversed by the use of β-cyclodextin. It is also said to teach the tabun is not reversed even though it is of a similar structure to sarin, concluding that the art is not predictable.

It is respectfully submitted that the invention as claimed is fully enabled and predictable The depolarizing and non-depolarizing neuromuscular blocking agents for which the invention is to reverse act by reversible binding. According to the method of the invention, the concentration of neuromuscular blocking agent in circulation is lowered and, consequently, bound neuromuscular blocking agent is released from acetylcholine receptors and muscle function is returned.

The nerve agents disclosed by DÉSIRÉ et al are reactive phosphonylating agents that cause irreversible inhibition of acetylcholinesterases throughout the body. Since the normal function of these enzymes is to hydrolyse acetylcholine, inhibition of these enzymes results in the accumulation in excessive concentration of acetylcholine and its various sites of action. The accumulation of the excess acetylcholine produces

the physiological results of these toxins. These nerve agents also increase the acetylcholine concentration in the neuromuscular junction of skeletal muscle that initially causes muscular fasciculations (twitches), followed by muscle weakness and then finally flaccid paralysis. These agents act by irreversible inhibition of the acetylcholinesterases by phosphorylating the enzymes and their action cannot be reversed. Accordingly, the effect of the cyclodextrins as catalysts for the inactivation, i.e., irreversible hydrolysis, of the nerve agents studied by DÉSIRÉ are functions different from the methods for reversal presently claimed. The predictably with respect to catalytic function of cyclodextrins on these nerve agents suggests nothing about the predictably of the chemical chelators used for reversing the drug-induced neuromuscular blockage by non-depolarizing and depolarizing neuromuscular blocking agents according to the present invention. Following the claimed method for reversing the defined types of neuromuscular blocking agents, the ordinary practitioner would not have to undergo undue experimentation to practice the invention. Accordingly, it is respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be withdrawn.

Claims 11-13 stand rejected under 35 U.S.C. 103(a) for being obvious over DÉSIRÉ et al. DÉSIRÉ et al is relied on for teaching that sarin and soman are inactivated by cyclodextrins in vitro. The Examiner acknowledges that the reference does not

specifically exemplify actual administration of a cyclodextrin to a subject, but suggests such administration. The Examiner concluded that it would have been obvious to one of ordinary skill in the art to administer a cyclodextrin to a subject to reverse the neuromuscular effect induced by sarin or soman, and would be motivated to employ a cyclodextrin for this method based on the teaching of DÉSIRÉ et al.

Rejection of claims 11-13 over DÉSIRÉ et al is respectfully traversed. As discussed above, the action of cyclodextrins in the mechanism of DÉSIRÉ et al is that of a catalyst to hydrolize the nerve agents. It is not acting as a chelator to form a complex, as in the method of the present invention.

As set forth in Figure 1 of DÉSIRÉ et al, the catalytic mechanism contains three steps, first, a complex formation between cyclodextrin and the nerve agent, followed by phosphonylation of this cyclodextrin, and finally dephosphonylation leading to the hydrolysed nerve agent. As mentioned, the cyclodextrins only successively catalyze the inactivation of sarin and soman, but not tabun and VX. The reason for the lack of catalytic inactivation in tabun and VX was not determined, but it can be concluded that DÉSIRÉ et al only teach that the hydrolysis of certain nerve agents can be catalyzed by cyclodextrins. However, they do not teach that the neuromuscular blocking effect of the depolarizing and non-depolarzing agents used in the present invention, without

increasing the level of acetylcholine in a patient, may be reversed by the use of β-cyclodextin.

The present invention is directed to reversibly displacing a neuromuscular blocking agent from its binding site at a acetylcholine receptor. The ordinary practitioner reviewing DÉSIRÉ et al, would not conclude that cyclodextrins, for example, would have this function. Accordingly, it is respectfully submitted that this reference does not render obvious the claimed method for reversing drug-induced neuromuscular blockage in a patient by a depolarizing or non-depolarizing neuromuscular blocking agent without causing an increase in the level of acetylcholine.

Claims 11-14 stand rejected under the judicially created doctrine of obviousness-type double patenting over claim 9 of U.S. Patent 6,670,340, which is said to recite a method for reversing neuromuscular blockage using mercaptocyclodextrins. On allowance of the claims in the present applications, applicants will submit a timely terminal disclaimer with respect to claim 9 of U.S. Patent 6,670,340.

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